there was a significant positive correlation between delta eGFR and ribavirin serum concentration, and the ribavirin serum concentration at week 1 was negatively correlated with the Hb levels from week 2 to week 8 [5]. Although the exact mechanisms are still not completely understood, all together, these data suggest that telaprevir and boceprevir can impair renal function early in the course of triple therapy for hepatitis C infection, and that this impairment can lead to ribavirin accumulation and can explain, at least in part, the higher rates of anemia observed in triple *vs.* double therapy. On the base of these evidences, we think that renal function should be assessed not only before, as already recommended, but also early after the beginning of triple therapy (1–2 weeks), that those patients experiencing a decline of eGFR should be strictly monitored, and that an early reduction of ribavirin dose should be strongly considered at least in patients experiencing a reduction of eGFR to <60 ml/min.

Conflict of interest

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References

[1] Romero-Gómez M, Berenguer M, Molina E, Calleja JL. Management of anemia induced by triple therapy in patients with chronic hepatitis C: Challenges, opportunities and recommendations. J Hepatol 2013;59:1323–1330.
[2] Mauss S, Hueppe D, Alshuth U. Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. Hepatology 2013;59:46–48.
[3] Kapelusznik L, Majid AM, Cox ER, Funk E, Flores Y, Charon B, et al. Boceprevir is associated with a decline in renal function in a cohort of HCV-treated patients. J Hepatol 2013;58:s342.
[4] Fukuda K, Imai Y, Hiramatsu N, Irishio K, Igura T, Sawai Y, et al. Renal impairment during the treatment of telaprevir with peginterferon and ribavirin in patients with chronic hepatitis C. Hepatol Res 2013. http://dx.doi.org/10.1111/hepr.12229 [Epub ahead of print].
[5] Karino Y, Ozeki I, Hige S, Kimura M, Arakawa T, Nakajima T, et al. Telaprevir impairs renal function and increases blood ribavirin concentration during telaprevir/pegylated interferon/ribavirin therapy for chronic hepatitis C. J Viral Hepat 2013. http://dx.doi.org/10.1111/jvh.12162 [Epub ahead of print].
[6] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405–2416.
[7] McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhai NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362:1292–1303.
[8] Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195–1206.
[9] Flamm SL, Lawitz E, Jacobson I, Bourliere M, Hezode C, Vierling JM, et al. Boceprevir with peginterferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. Clin Gastroenterol Hepatol 2013;11:81–87.
[10] Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, et al. CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) – NCT01514890. J Hepatol 2013;59:434–441.

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Reply to: “Renal impairment and anemia during triple therapy”

To the Editor:
We appreciate the comment by Vespasiani-Gentilucci *et al.* about renal impairment and anemia during hepatitis C treatment with protease inhibitors. We agree with the authors that renal impairment is a growing concern in these patients, although the prevalence of estimated glomerular filtration rate (eGFR) <60 ml/min does not seem to be significantly high with these drugs (6.6% with boceprevir and 4.7% with telaprevir [1]). Additionally to protease inhibitors, older age, arterial hypertension, high baseline serum creatinine as well as type 2 diabetes mellitus were found to be associated with anemia [2]. Probably, the link between these factors and anemia is the appearance of renal impairment [3]. Indeed, the mechanisms involved in renal impairment with protease inhibitors remain poorly understood. Significant inhibition of some human renal drug transporters that could influence ribavirin serum concentration has been described with telaprevir [4]. This has been correlated with delta eGFR [5]. Telaprevir though has shown an acceptable tolerability in haemodialyzed patients who were listed for kidney transplantation, managing successfully anemia with erythropoietin and ribavirin dose reductions [6]. On the other hand, mean boceprevir concentration was comparable in patients with end-stage renal disease and in healthy subjects [7]. In conclusion, there is a mild risk of renal insufficiency stage 3 with protease inhibitors that could be responsible, at least in part, of the anemia that develops during triple therapy. Thus, renal function should be closely monitored to anticipate the appearance of anemia.

Conflict of interest

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References

[1] Mauss S, Hueppe D, Alshuth U. Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. Hepatology 2014, [Epub ahead of print].
[2] Crismale JF, Martel-Laferrière V, Bichoupan K, Schonfeld E, Pappas A, Wyatt C, et al. Diabetes mellitus and advanced liver fibrosis are risk factors for severe

anaemia during telaprevir-based triple therapy. Liver Int 2013. http://dx.doi.org/10.1111/liv.12342. [Epub ahead of print].
[3] Hörl WH. Anaemia management and mortality risk in chronic kidney disease. Nat Rev Nephrol 2013;9:291–301.
[4] Kunze A, Huwyler J, Camenisch G, Gutmann H. Interaction of the antiviral drug telaprevir with renal and hepatic drug transporters. Biochem Pharmacol 2012;84:1096–1102.
[5] Karino Y, Ozeki I, Hige S, Kimura M, Arakawa T, Nakajima T, et al. Telaprevir impairs renal function and increases blood ribavirin concentration during telaprevir/pegylated interferon/ribavirin therapy for chronic hepatitis C. J Viral Hepat 2013. http://dx.doi.org/10.1111/jvh.12162. [Epub ahead of print].
[6] Dumortier J, Guillaud O, Gagnieu MC, Janbon B, Juillard L, Morelon E, et al. Anti-viral triple therapy with telaprevir in haemodialysed HCV patients: is it feasible? J Clin Virol 2013;56:146–149.
[7] Treitel M, Marbury T, Preston RA, Triantafyllou I, Feely W, O'Mara E, et al. Single-dose pharmacokinetics of boceprevir in subjects with impaired hepatic or renal function. Clin Pharmacokinet 2012;51:619–628.

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Evidence recommending antiviral therapy in hepatitis C

To the Editor:

Recently, Dr. Van der Meer and colleagues [1] discussed our systematic review of trials comparing interferon monotherapy to no therapy for retreating individuals infected with hepatitis C virus who had not achieved a sustained virological response (SVR) from previous antiviral therapy [2]. Our review made several observations: (1) retreatment with interferon monotherapy provided no relevant clinical benefit; (2) while there was a statistically significant reduction in non-fatal variceal bleeding, the number needed to treat (NNT) was so high (NNT = 67) that the treatment is economically unfeasible; (3) when only the low risk of bias trials were considered, interferon treatment increased all-cause mortality; (4) the recipients of interferon had more adverse events; and (5) the commonly used surrogate outcome of SVR occurred significantly more often in the treated group.

Since interferon treatment increased SVRs without improving clinical outcomes, the SVR was not a valid surrogate outcome in this scenario. As such, SVR cannot be universally considered as valid for purposes of clinical practice. We believe that, before it can be considered a trustworthy surrogate outcome in other scenarios, it must be validated in those scenarios, or at least in enough other scenarios that the single example of retreatment of interferon monotherapy could be considered to be an outlier.

Validation of a surrogate outcome is a two-step process [3]. First, there has to be a strong and consistent association between the surrogate outcome and the clinical one. However, association alone is not adequate to establish validation. It also has to be shown that improving the surrogate outcome also similarly improves the clinical one; in other words, a treatment-related difference between the study groups in the surrogate outcome should be associated with a proportionate treatment-related difference in the clinical outcome. This latter step can only be demonstrated in randomized clinical trial (RCTs). Most RCTs assessing hepatitis C antiviral therapy do not provide clinical outcomes, presumably because these outcomes require years to pass before they begin to appear. Thus, there are limited data available to assess the validity of the SVR. Of note, several other Cochrane reviews also found scenarios in which an improved SVR did not translate into a meaningful beneficial clinical outcome These included comparing interferon with or without ribavirin [4], using ribavirin alone [5], and employing interferon in treatment-naïve patients [6]. Dr. van der Meer and his colleagues cited two of these [4,6], but only noted that the improvement in SVR was accompanied by improvement in liver histology (another surrogate). Not mentioned by van der Meer *et al.*, adding ribavirin to interferon resulted in a minimal but statistically significant reduction in the combined endpoint of death and hepatic morbidity (0.28% reduced to 0.12%), but the NNT was 625 (compared to an NNT of 4 for achieving an SVR) [4].

Van der Meer *et al.* appeared to be most concerned with our statement that the presence of treatment harm and the failed validation of SVRs "should caution us to stop advocating antiviral interventions of any kind until we have evidence of clinical efficacy and cost-effectiveness" [2]. To support their argument that SVR is a good outcome to assess antiviral therapy, they cite a number of lines of evidence that demonstrate the association between SVR and good outcomes. We agree with them that the SVR is a good prognostic sign. However, the key issue is that the SVR has not been validated as a surrogate outcome. In other words, there are no RCTs that have shown that a treatment that increases the number of SVRs equates with improved clinical outcomes. Van der Meer *et al.* agree that this is the case.

We and van der Meer *et al.* also agree that most infected patients will not develop decompensated liver disease or hepatocellular carcinoma and that the prognostic factors identifying patients who are likely to achieve an SVR are also factors that